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ORIGINAL ARTICLE

Gastroenterology

Effect of glycerin on colonic motility in children

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Abstract

Objective: Colonic manometry (CM) involves measurement of colonic neuromuscular activity and administration of a stimulant laxative, most commonly bisacodyl, which is part of the study protocol. Glycerin is another laxative used in the treatment of constipation. Our objective was to evaluate the effect of glycerin on colonic motility and compare the response to glycerin with each patient's response to bisacodyl.

Methods: We performed a retrospective review of all CM studies performed between May 2015 and May 2022. All studies with glycerin administration were included. Patient demographics, medical and surgical history, and results of each CM, including name, number, and dose of stimulant laxatives administered, colonic motor response after each stimulant, and final interpretation, were recorded.

Results: We included 131 CM studies in 125 patients (53% female, median age at CM 10 years, interquartile range 7–14 years). Compared to bisacodyl, glycerin more commonly triggered fully propagated high-amplitude propagating contractions (HAPCs; 35% vs. 13%, $p < 0.001$) and led to a greater extent of propagation (propagation to sigmoid vs. to descending colon, $p < 0.001$). In 36% of studies, glycerin led to an improved response (stimulation of HAPCs when they were absent after bisacodyl, or HAPCs propagating through a greater extent of colon) compared to bisacodyl. In studies with an improved response, the median dose of glycerin in mL/kg was not significantly different compared to studies with the same/worse response.

Conclusion: Glycerin can trigger HAPCs in patients in whom bisacodyl was not able to do so. Incorporation of glycerin into standard CM protocols should be considered.

KEYWORDS
bisacodyl, colonic manometry, high-amplitude propagating contractions, pediatrics

1 | INTRODUCTION

Colonic manometry (CM) is considered as the standard diagnostic modality in the workup of children with constipation refractory to conventional treatment to diagnose colonic dysmotility.[1] With the use of a manometry catheter, the colonic neuromuscular function is evaluated by the measurement of intraluminal pressure as well as interpreting the morphology and coordination of pressure waves.[2] High-amplitude

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propagating contractions (HAPCs) are the most recognizable and clinically significant pressure waves observed in CM testing. The presence of HAPCs is indicative of an intact neuromuscular function of the colon. Propagation of HAPCs that terminate prematurely (i.e., before reaching the distal sigmoid colon) may indicate segmental colonic dysmotility, while total absence of HAPCs throughout the colon suggests colonic inertia.[2,3] The standard CM protocol consist of three phases: the fasting phase, postprandial phase, and stimulant phase with colonic stimulation by intraluminal administration of the stimulant laxative bisacodyl given its ability to induce HAPCs.[2,4,5] It has been shown that an additional dose of bisacodyl can induce HAPCs in patients who did not have HAPCs with the first dose, suggesting a possible additive effect.[6] Bisacodyl has a dual-action mechanism since it is a prokinetic agent that stimulates sensory nerve endings to increase colonic peristalsis as well as a secretory agent that inhibits intestinal water absorption and is widely used in the management of children with constipation.[7,8] If after bisacodyl administration, an inadequate response in colonic motility is seen, a dose of glycerin is given at our institution. Glycerin, a trihydroxy sugar alcohol, which acts as both an osmotic and stimulant laxative, has been successfully used in antegrade enemas and as a rectal medication.[9] Our objectives were to evaluate the effect of glycerin on colonic motility and to compare the response induced by both bisacodyl and glycerin in children undergoing CM.

What is Known?

- Colonic manometry (CM) involves measurement of colonic motor activity after administration of a stimulant laxative, most commonly bisacodyl.
- Bisacodyl has the ability to induce high-amplitude propagating contractions (HAPCs).
- Some patients do not have a colonic motor response after two doses of bisacodyl.

What is New?

- Glycerin can trigger HAPCs in patients in whom bisacodyl was not able to do so.
- Glycerin led to more fully propagated contractions than bisacodyl did.
- Incorporation of glycerin into standard CM protocols should be considered.

2 | METHODS

We performed a single-center, retrospective review of all CM studies performed at Nationwide Children's Hospital between May 2015 and May 2022. The Nationwide Children's Hospital Institutional Review Board approved the study protocol (STUDY00000932). All studies in which glycerin was administered during the stimulant phase of the CM were included. Data on patient demographics, medical and surgical history, and results of CM testing were recorded. Recorded measures of CM included the name, number, and dose of stimulant laxatives administered during the study, colonic motor response after each stimulant administration (post-bisacodyl and post-glycerin), and the final interpretation of each study. To compare the distal length of propagating HAPCs through the colon after bisacodyl and glycerin, we separated colonic landmarks into six categories (1 = no propagation, 2 = propagation to ascending colon, 3 = propagation to transverse colon, 4 = propagation to descending colon, 5 = propagation to sigmoid, and 6 = full propagation); the further HAPCs propagate, the higher the value (Supporting Information S1: Supplement A). If two doses of bisacodyl were given, the best response to bisacodyl (response with furthest propagation of HAPCs) was used. To compare the stimulant responses, we categorized the colonic motor responses after glycerin as *improved* if there was stimulation of HAPCs when they were absent after bisacodyl, or if HAPCs subsequently propagated through a greater extent of colon compared to bisacodyl. Colonic motor responses were categorized as *worsened* if propagation of HAPCs was less than that after the administration of bisacodyl. No change in colonic motor response between stimulants was categorized as *same* response. All CM studies were reviewed by two pediatric gastroenterologists specialized in gastrointestinal motility disorders, specifically for this study. Reviewers were not blinded to timing and type of pharmacotherapy administered and all analyses of manometric data were performed using a commercially available manometric system (Solar GI HRM v9.1, Medical Measurement Systems).

2.1 | CM testing

CM was performed with the use of either a high-resolution solid-state catheter (Unisensor AG, Attikon) or a water-perfused catheter (Medical Measurement Systems) following current guidelines and the department's protocol.[2] On the day(s) before the study, children completed a bowel clean out with a combination of polyethylene glycol 3350 and stimulant laxatives, usually bisacodyl. On the day of CM testing, the manometry catheter was placed either using colonoscopy or with fluoroscopic guidance by an interventional radiologist. Following placement, an abdominal x-ray was performed to confirm the catheter's position. After a recovery period, manometric data were recorded during the fasting phase (lasting at least 1 h), postprandial phase (during and after a meal, lasting at least 2 h), and after administration of stimulant laxatives, typically one or two doses of bisacodyl 0.2 mg/kg (maximum of 10 mg) and one additional dose of glycerin (generally 10 mL for children and 20 mL for adolescents, however the dose may vary if glycerin, in a specific dose, is part of patient's flush regimen). If inadequate colonic motility (absent HAPCs, only one HAPC, or not fully propagating HAPCs without urge sensation or stool output) was seen after the first dose of bisacodyl, a second dose of bisacodyl or glycerin was given. Time between administrations of the different doses was at least 1 h.

2.2 | Statistical analyses

Categorical data are presented as frequencies and percentages, while non-normally distributed continuous data are presented as medians and interquartile ranges (IQRs). Differences between groups were analyzed using Fisher's exact test or the Mann–Whitney *U* test as appropriate. A *p* value less than 0.05 was considered statistically significant. Statistical analyses were conducted with SPSS for Windows, version 28.0.0.0 (SPSS, Inc.).

3 | RESULTS

Between May 2015 and May 2022, 555 CM studies were performed in a total of 503 patients. Among these, glycerin was administered during the stimulant phase in 131 CM studies in 125 patients (53% female, median age at CM 10 years, IQR 7–14 years). Patient characteristics are shown in Table 1. The median duration of symptoms at the time the CM was performed was 6 years (IQR 4–9). The most common underlying diagnoses of the patients undergoing CM included functional constipation (78%), tethered spinal cord (10%), Hirschsprung disease (9%), and irritable bowel syndrome (9%). Fifty-four percent of patients had no surgical history. High-resolution solid-state catheters were used in 89% ($n = 117$) of the studies, water-perfused catheters in 8% ($n = 10$), and in 3% ($n = 4$) both type of catheters (one placed antegrade via cecostomy or appendicostomy and one retrograde) were used. Catheter placement was performed through rectum in 90% ($n = 118$) of the studies, through cecostomy/appendicostomy in 5% ($n = 6$), through both rectum and cecostomy/appendicostomy in 5% ($n = 6$), and through colostomy in 1% ($n = 1$). The median dose of the first bisacodyl was 0.24 mg/kg (IQR 0.17–0.34). In 31% ($n = 40$) of the studies, patients received a second dose of bisacodyl before glycerin administration, with a median of 0.30 mg/kg (IQR 0.18–0.40). The median dose of glycerin was 0.53 mL/kg (IQR 0.37–0.79). Final interpretation of CM studies after one or two doses of bisacodyl and one dose of glycerin were as follows: distal colonic dysmotility in 45% ($n = 59$), normal colonic motility in 35% ($n = 46$), colonic inertia in 18% ($n = 23$), proximal colonic dysmotility in 2% ($n = 2$), and retrograde contractions in 1% ($n = 1$).

TABLE 1 Patient characteristics ($n = 125$).

	Patients ($n = 125$)
Age in years at CM, median (IQR)	10 (7–14)
Sex, *n* (%)	
Female	66 (53)
Male	59 (47)
Weight in kg, median (IQR)	34 (22–54)
Race, *n* (%)	
White	106 (85)
Black	11 (9)
Latino/Hispanic	2 (2)
Asian	1 (1)
Bi-racial/multi-racial	1 (1)
Unknown	4 (3)
Duration of symptoms in years, median (IQR)	6 (4–9)
Medical history, *n* (%)[a]	
Functional constipation	98 (78)
Tethered spinal cord	12 (10)
Hirschsprung disease	11 (9)
Irritable bowel syndrome	11 (9)
Anorectal malformation	3 (2)
Pediatric intestinal pseudo-obstruction	2 (2)
Surgical history, *n* (%)[a]	
None	68 (54)
Cecostomy	18 (14)
Diverting ostomy	15 (12)
Appendicostomy	14 (11)
Colonic resection	13 (10)
Pull-through procedure	10 (8)
Tethered cord release	8 (6)
Sacral nerve stimulation insertion	5 (4)
Anorectal malformation repair	3 (2)

Abbreviations: CM, colonic manometry; IQR, interquartile range.
[a]Some patients do have more than one.

TABLE 2 Comparison of colonic motor response to bisacodyl and glycerin during colonic manometry testing ($n = 131$).

	Bisacodyl ($n = 131$)	Glycerin ($n = 131$)	p
Colonic motor response, n (%)			
Fully propagating HAPCs	17 (13)	46 (35)	<0.001*
HAPCs terminating in sigmoid colon	44 (34)	43 (33)	1.000
HAPCs terminating in descending colon	15 (11)	10 (8)	0.401
HAPCs terminating in transverse colon	6 (5)	4 (3)	0.749
HAPCs terminating in ascending colon	2 (2)	2 (2)	1.000
No HAPCs	43 (33)	24 (18)	0.010*
Segmental distal HAPCs	4 (3)	2 (2)	0.684
Propagation			
Propagation of HAPCs, median (IQR)[a]	4 (1–5)[b]	5 (4–6)[b]	<0.001*

Abbreviations: HAPC, high-amplitude propagating contraction; IQR, interquartile range.

[a]1 = no propagation, 2 = propagation to ascending colon, 3 = propagation to transverse colon, 4 = propagation to descending colon, 5 = propagation to sigmoid, and 6 = full propagation.

[b]$n = 125$, $n = 6$ that showed segmental distal HAPCs were excluded.

*Denotes p value < 0.05.

TABLE 3 Comparison of studies with fully propagating HAPCs versus non-fully propagating HAPCs after bisacodyl and glycerin ($n = 131$).

	Fully propagating HAPCs	Non-fully propagating HAPCs	p
Bisacodyl	$n = 17$	$n = 114$	
Daily use of bisacodyl at time of CM, n (%)	7 (41)	49 (43)	1.000
Duration of symptoms in years, median (IQR)	10 (6–12)	10 (7–15)	0.683
Functional constipation, n (%)[a]	13 (77)	83 (73)	1.000
History of colorectal surgery, n (%)	8 (47)	55 (48)	1.000
Glycerin	$n = 46$	$n = 85$	
Daily use of glycerin at time of CM, n (%)	8 (17)	19 (22)	0.652
Duration of symptoms in years, median (IQR)	7 (3–9)	6 (4–9)	0.586
Functional constipation, n (%)[a]	33 (72)	63 (74)	0.837
History of colorectal surgery, n (%)	22 (48)	41 (48)	1.000

Abbreviations: CM, colonic manometry; HAPC, high-amplitude propagating contraction; IQR, interquartile range.

[a]No other organic underlying disease, for example, tethered spinal cord, Hirschsprung disease, anorectal malformation, or pediatric intestinal pseudo-obstruction.

As shown in Table 2, glycerin was more likely to lead to fully propagated HAPCs compared to bisacodyl (35% vs. 13%, $p < 0.001$). When looking to the extent of propagation of HAPCs ($n = 125$, excluded $n = 6$ with segmental distal HAPCs), glycerin also led to a greater extent of propagation compared to bisacodyl dose(s): propagation to sigmoid (5) versus propagation to descending colon (4), $p < 0.001$. In Table 3, studies with fully propagating HAPCs are compared with studies with non-fully propagating HAPCs after bisacodyl as well as after glycerin administration. No significant difference in daily use of bisacodyl at time of CM was seen when studies with fully propagating HAPCs ($n = 17$) were compared with studies with non-fully propagating HAPCs ($n = 114$) after administration of bisacodyl (41% vs. 43%, $p = 1.000$). Median duration of symptoms in years at time of CM was also not significantly different between studies with fully propagating HAPCs and studies with non-fully propagating HAPCs after administration of bisacodyl (10 years vs. 10 years, $p = 0.683$). Similarly, daily use of glycerin at time of CM was not significantly different between studies with fully propagating HAPCs ($n = 46$) and studies with non-fully propagating HAPCs ($n = 85$) after administration of glycerin (17% vs. 22%, $p = 0.652$). Median duration of symptoms in years at time of CM was also not significantly different between studies with fully propagating HAPCs and studies with non-fully

TABLE 4 Comparison of studies with an *improved* glycerin colonic motility response compared to the preceding bisacodyl response versus studies with the *same* or *worse* response ($n = 131$).

	Improved response after glycerin ($n = 47$)	Same or worse response after glycerin ($n = 84$)	p
Age in years, median (IQR)	14 (8–16)	9 (6–12)	<0.001*
Duration of symptoms in years, median (IQR)	8 (4–12)	6 (3–8)	0.024*
Functional constipation, n (%)[a]	34 (72)	62 (74)	0.840
History of colorectal surgery, n (%)	19 (40)	44 (52)	0.206
Daily use of bisacodyl at time of CM, n (%)	18 (38)	38 (45)	0.467
Daily use of glycerin at time of CM, n (%)	8 (17)	19 (23)	0.506
Dose glycerin in mL/kg used during CM, median (IQR)	0.48 (0.30–0.79)	0.55 (0.35–0.84)	0.581

Abbreviations: CM, colonic manometry; IQR, interquartile range.

[a]No other organic underlying disease, for example, tethered spinal cord, Hirschsprung disease, anorectal malformation, or pediatric intestinal pseudo-obstruction.

*Denotes p value < 0.05.

propagating HAPCs after administration of glycerin (7 years vs. 6 years, $p = 0.586$). For the response after bisacodyl as well as for the response after glycerin, when studies with fully propagating HAPCs were compared with studies with non-fully propagating HAPCs, no significant differences were found based on underlying medical history or history of colorectal surgery (Table 3).

In 36% ($n = 47$) of the studies, the glycerin colonic motility response was improved (stimulation of HAPCs when they were absent after bisacodyl, or HAPCs subsequently propagating through a greater extent of colon compared to bisacodyl) compared to the preceding bisacodyl response. In 60% ($n = 79$), the colonic response to glycerin was the *same*, and in 4% ($n = 5$), the response was *worse* when compared to bisacodyl. As shown in Table 4, the median age (14 years vs. 9 years, $p < 0.001$) and duration of symptoms (8 years vs. 6 years, $p = 0.024$) of patients with studies with an *improved* response to glycerin were significantly higher compared to studies with the *same* or *worse* response. No significant differences in underlying medical history (72% vs. 74%, $p = 0.840$), history of colorectal surgery (40% vs. 52%, $p = 0.206$), daily use of bisacodyl at time of CM (38% vs. 45%, $p = 0.467$), daily use of glycerin at time of CM (17% vs. 23%, $p = 0.506$), and median dose of glycerin in ml/kg during CM (0.48 vs. 0.55, $p = 0.581$) were found when studies with an *improved* response were compared with studies with the *same* or *worse* response (Table 4).

4 | DISCUSSION

This study shows that glycerin is an effective stimulant to enhance colonic motility in children during CM studies. Glycerin triggered HAPCs in patients in whom bisacodyl was not able to do so, and it led to a significantly higher proportion of fully propagating HAPCs compared to bisacodyl. No significant differences in underlying medical history, history of colorectal surgery, and daily use of bisacodyl (orally, in flushes or rectally) or glycerin (in flushes or rectally, not available orally) at time of CM were found when studies with an *improved* response to glycerin were compared to those with the *same* or *worse* response compared to the preceding bisacodyl response. Additionally, the median doses of glycerin administered during the CM were not significantly different between these two groups.

In a recent prospective single-center cross-over study with 45 patients aged 2–18 years comparing bisacodyl to glycerin, bisacodyl was found to generate more HAPCs compared to glycerin and the HAPCs after bisacodyl had a longer duration of action and longer propagation.[10] No significant difference in amplitude or onset time was found.[10] There has also been evidence that an additional higher dose of bisacodyl (0.4 mg/kg compared to 0.2 mg/kg) can provoke a higher proportion of fully propagating HAPCs.[6] Our study shows another aspect of glycerin, where it is used as a next-line option in patients who have not responded to bisacodyl during manometry testing. Our results show that glycerin administration is associated with a significantly increased proportion of fully propagating HAPCs in these patients compared with their bisacodyl response alone. This allows for further in-depth analysis when undergoing this procedure, especially in patients with refractory constipation that have not responded to other treatments. Another stimulant agent that can provoke HAPCs can provide additional information and help guide future treatments. For patients who did not respond to bisacodyl during CM, but did respond to glycerin, changing their medication to or start glycerin (e.g., in antegrade flushes) in the first place, could be considered.

The administration of glycerin after bisacodyl in our study raises the question of whether glycerin resulted in a better response due to an additive or synergistic effect. In terms of pharmacodynamics, bisacodyl produces HAPCs 15–60 min after rectal administration and within 60 min after intraluminal colonic administration.[7] Often, intraluminal bisacodyl acts within 10 min, and it can be characterized as one or more HAPCs within 12 min of infusion.[4,11] It acts locally when infused intraluminally, which is done through the manometry catheter during motility testing. In addition, based on limited animal data, the secretory function of bisacodyl reaches its peak 25 min after administration.[12] In our study, glycerin administration was at least 1 h after bisacodyl administration, making it is less likely that an additive effect occurred. Regarding glycerin's pharmacodynamics, suppositories act within 15–30 min, while intraluminal injection into the colon stimulates activity within 2–5 min.[13,14] The 1-h time gap likely allowed for differentiation between the effects of the two stimulants. Further studies comparing coadministration of bisacodyl and glycerin simultaneously may be valuable in determining if there is an additive or synergistic effect.

Based on our data, daily use of bisacodyl at time of CM did not have an effect on the colonic motor response after bisacodyl administration during CM testing. In addition, daily use of bisacodyl in children who had an *improved* response after glycerin compared to the preceding bisacodyl response was not significantly different from children who had the *same* or *worse* response. Hence, a tachyphylaxis mechanism based on receptor desensitization due to chronic exposure to a drug does not appear to explain why bisacodyl did not stimulate a good motor response. Children who had an *improved* response after glycerin were significantly older (14 years vs. 9 years, $p < 0.001$) and had significantly longer duration of symptoms (8 years vs. 6 years, $p = 0.024$) compared to children who had the *same* or *worse* response. Typically, older children have experienced symptoms for a longer period. However, it is not known why older children or those with a longer duration of symptoms exhibit a better response to glycerin. Further research is needed to understand the underlying mechanisms that contribute to this improved response.

The American Neurogastroenterology and Motility Society and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guideline for CM includes three phases for data collection during the procedure: fasting phase, postprandial phase, and stimulant phase. The protocol for performing and interpreting CM is however not standardized and can vary widely between institutions. In our institution, if there are no HAPCs during the postprandial phase, bisacodyl (0.1–0.2 mg/kg) is administered intraluminally through the manometry catheter to provoke HAPCs.[2] Bisacodyl is the first-line stimulant used because it can produce HAPCs similar to physiologic post-prandial HAPCs.[4] However, our study has shown that glycerin is capable of producing HAPCs as well, particularly in patient populations where bisacodyl was not able to elicit colonic contractions. It is worthwhile to consider it as another option for the stimulant phase in future manometry protocols. Additionally, our study showed that the effectiveness of glycerin is not necessarily dose-dependent since median doses were not significantly different among responses. Incorporating a standardized dose of glycerin within the median dose values seen in Table 4 (0.48–0.55 mL/kg) as another option in manometry algorithms may be worth considering. Furthermore, in terms of the final interpretation of CM studies, it may be useful to further refine normal colonic motility results by adding the “normal colonic motility with high-dose stimulants”-category if a patient only responded to multiple doses of stimulant laxatives. The colon was in the end still capable of producing HAPCs, which is a crucial observation as it effectively excludes colonic inertia as a diagnosis. However, we do believe that there should be a distinction between a study with normal HAPCs after one dose of bisacodyl versus one that requires another dose of bisacodyl and/or a dose of glycerin. Moreover, it suggests that, for these patients, glycerin may be a more suitable treatment option than bisacodyl.

Limitations of our study are inherent to its retrospective design. We were unable to have complete standardization of the doses of stimulants that the patients received, nor were we able to compare glycerin effects before any doses of bisacodyl were administered providing room for selection bias. We also did not include colonic propagations that were limited to distal segments of the colon. This could be an important point to study in the future. Since distal colonic dysmotility is much more common than proximal colonic dysmotility, clinical correlation with these segmental propagation results may be warranted to guide management.

5 | CONCLUSION

In conclusion, when glycerin was used as a second-line agent during CM in pediatric patients, it led to more fully propagated contractions than bisacodyl did as a primary stimulant. Additionally, glycerin was effective in triggering HAPCs in patients where bisacodyl failed to do so. Our data support the idea that the incorporation of glycerin into CM protocols, specifically as an additional agent when bisacodyl is not effective, should be considered.

CONFLICT OF INTEREST STATEMENT

Julia M. J. van der Zande received financial support from the Cultuurfonds, with support from the

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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